REMARKS/ARGUMENTS

The specification has been revised at pages 25 and 27 to remove text containing a "http://" indication followed by a URL address. The change on page 25 also includes correction of a typographical error.

Claim 15 has been revised by inclusion of a final clause which repeats the content from the preamble and the first subparagraph of the claim. Support for this change is provided throughout the application as filed, such as by the above mentioned portions of the claim as well as page 6, second paragraph, of the specification. Additionally, claim 15 has been revised to include subject matter from claim 1 and claim 19 as originally filed. These claims, in addition to at least page 18, first full paragraph of the specification, support these changes to claim 15. These changes are made for business considerations and to better tailor the claims to encompass commercially contemplated embodiments of the invention at the present time. The amendments are not in acquiescence to any rejection of record.

Claim 18 has been revised to use alternate language for the same concept.

Claim 19 has been amended to remove the dependency from claim 1 as originally filed and with a revision to describe what is inherently present on a microarray. Beyond claim 1, additional support is provided at least on pages 10-11, bridging paragraph. Claim 30 has been revised in a similar fashion.

Claim 20 has been re-written in independent form, which is supported at least by claim 15. Claim 21 has been revised to correct a clerical error.

New claims 33-48 have been introduced. Claims 33-36 are supported at least by original claim 19. Claims 37 and 38 are supported at least by original claims 25 and 26 as well as pages 14-15, bridging paragraph. Claims 39-41 are supported at least by original claim 20. Claims 42-43 are supported at least by original claims 13 and 14. Claims 44-46 and 47-48 are supported at least by claims 16-18 and 31-32, respectively.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Restriction Requirement

Applicants acknowledge the withdrawal of claims 1, 3, 4, 7-14, and 22-29 from consideration. Applicants expressly reserve all rights to pursue, without prejudice, the subject matter of these claims in a continuing or divisional application. The withdrawal of these claims has no effect on the scope of claims 15-21 and 30-32 under examination.

Claim Objections

Claim 19 was objected to as depending on withdrawn claim 1. Applicants respectfully point out that claim 19 has been amended to remove the dependency from claim 1. Applicants respectfully submit that this objection has been overcome and may be withdrawn.

Specification

The specification was objected to as containing an embedded hyperlink and/or other form of browser-executable code. Applicants respectfully point out that the specification on pages 25 and 27 has been revised without changing the content of the description. Applicants respectfully submit that this objection has been overcome and may be withdrawn.

Claim Rejections under 35 USC § 112, first paragraph

Claims 15-21 and 30-32 were rejected under 35 USC § 112, first paragraph as allegedly "failing to comply with the written description requirement." Specifically, the statement of the instant rejection alleges that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of an inadequate written description has been presented.

As an initial matter, Applicants point out that the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement (Federal Register Vol. 66, No.4, 1099 January 5, 2001), include the guidance that

> "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." (see page 1105, left column and the case law cited therein).

The statement of the rejection, however, does not appear to acknowledge this presumption and asserts an inadequate written description based in part on a need for the instant application to "specifically identify the exact nucleotide sequences that are correlated with breast cancer". This requirement for specific sequences appears to be part of what is alleged to be needed to "convey possession of the claimed invention to one skilled in the relevant art".

Applicants respectfully point out, however, that this basis for the instant rejection appears to be at odds with the allegations of anticipation based upon Sioto et al. and Hung as addressed below. As the Federal Circuit set forth in *In re Donohue*,[1]

> "possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention."

Therefore, the allegations of anticipation by Sioto et al. and Hung must include the allegation that Sioto et al. and Hung place the instantly claimed invention in the possession of a skilled artisan provided with those teachings.

[1] 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985).

Applicants respectfully point out, however, that *neither Sioto et al. nor Hung provide any specific sequences for the "markers" they allegedly disclose for use in determining the stage of breast cancer of a given sample.* Therefore, and based upon the requirement asserted in the instant rejection, how could the disclosures of Sioto et al. or Hung have placed the instant invention in the possession of an artisan of ordinary skill?

Applicants respectfully suggest the consideration of the following: if, as alleged, the disclosure of Sioto et al. and Hung (lacking specific sequences) place the invention as claimed in the possession of a skilled artisan presented with those disclosure, how can the instant rejection require specific sequences for the claimed invention to be adequately described? Applicants point out that both Sioto et al. and Hung were issued within the last 12 months, during which the current standards for an adequate written description would have applied. In particular, Hung includes patented claims that encompass the use of nucleic acids encoding various proteins or portions thereof (see claim 4 for example) *without the disclosure of any sequences*. These proteins include ones which have no apparent human counterpart (for example the "Lg" protein described in column 7, lines 1-4, and found in claim 4, which refers to a hamster lacrimal gland female-specific major 20 kDa secretory protein as described in the attached abstract from Ranganathan et al.).

Thus, if Sioto et al. and Hung have, as alleged, placed the claimed invention in the possession of the skilled person without the need for specific sequences, the instant disclosure must, as a matter of logic, have similarly provided a similar adequate written description of the invention. If an adequate written description is not present for the instant claims despite the possession by the skilled person of the claimed invention based on the instant disclosure, there would be the anomalous result of the application placing the claimed invention in the hands of the skilled artisan but not in the hands of the Applicants. This is flawed logic that has no basis in U.S. patent law.

Moreover, and as noted in the instant application on page 7, last paragraph, the instant invention does not rely upon a particular specific sequence for its practice. Instead, it is the identity of the disclosed genes, rather than any specific sequences, that is required for the practice of the invention. This disclosure of the gene identities, with the correlation of their

expression to particular stages of breast cancer, is sufficient to place the invention in the possession of a skilled practitioner provided with the instant disclosure.

The sufficiency of the disclosure of gene identities is bolstered by the fact that the gene sequences are identified by reference to the IMAGE Consortium reference numbers. Those numbers reference specific individual polynucleotide molecules as deposited clones. It was these physical clones that were used to identify the genes suitable for use in the instant invention (see page 25, first full paragraph).

Thus while the sequences provided for each clone may be revised to make corrections, the actual physical polynucleotide molecules, and thus actual sequences thereof, remain unchanged. Therefore, the fact that a single clone may have multiple sequence accession numbers associated with it, such as multiple GenBank entries for the 5' end, the 3' end, and the full insert of a clone, is immaterial to the fact that the CloneID reference number refers to a specific physical polynucleotide molecule with a specific sequence.

Last, and to the extent that the instant rejection is directed to claims that do not reference any Table disclosed in the instant application, Applicants respectfully point out that claim 15 has been revised to refer to specific Tables for reasons unrelated to the instant rejection as explained above. Claim 20, however, has not been so revised and so Applicants respectfully traverse the instant rejection because a sufficient representative sampling of genes correlated with ADH, DCIS, and IDC has been provided by the instant application such that an adequate written description of the invention of claim 20 and new claims 39-43 has been provided.

As would be understood by the skilled person in the relevant art, the human transcriptome encompasses a finite number of expressed sequences. The instant invention is based upon the use of 11,435 gene sequences that were selected for the likelihood of their expression being relevant to breast cancer stages. Based upon this extensive study, relevant genes were identified and disclosed in the instant application. The sheer number of genes tested and then identified as useful in the instant invention counters the instant rejection's apparent requirement that an adequate description is not present for genes identified by their function instead of their structural features.

Such a requirement is that for an ***actual*** "reduction to practice" of identifying every gene sequence that would work in the instant rejection. Applicants respectfully and strongly traverse the instant rejection's reliance on this basis because no such requirement exists in U.S. patent law. To the contrary, it is well settled that U.S. patent law recognizes and permits **constructive reduction to practice** to support patentability.

In light of the above, the instant rejection is misplaced and should not have been made. Withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 USC § 112, second paragraph

Claims 15-21 and 30-32 were rejected under 35 USC § 112, second paragraph as allegedly indefinite for failing to "set forth steps to actually determine the stage of a breast cancer sample."

With respect to claims 15 and 30-32, the rejection alleges that there is "no step of analyzing the results of the assay and assigning a stage of breast cancer" in claim 15. Applicants respectfully disagree because the claims as originally presented clearly include "determining the breast cancer stage" of a sample by the assay method recited in the claim. Nevertheless, and in the interest of advancing prosecution, claim 15 has been revised to include this very aspect of "determining" without altering the scope of the claim. Applicants respectfully submit that this aspect of the rejection has been obviated and may be properly withdrawn.

With respect to claim 16, the instant rejection asserts that the claim does not refer to an action related to determining gene expression. Applicants respectfully point out that the necessary action is recited in claim 15 from which claim 16 depends. Accordingly, the rejection of claim 16 appears misplaced and may be withdrawn.

With respect to claims 18 and 19, the instant rejection has been obviated by the revisions to the claims to expressly recite inherent aspects of the use of an array to determine gene expression without altering the scope of the claims. Applicants respectfully submit that this aspect of the rejection has been obviated and may be properly withdrawn.

With respect to claim 20, Applicants point out that the claim has been revised to be in independent form without altering the scope of the claim. Applicants thank the Examiner for the recognition that it is possible for a single gene to be expressed in correlation with one or two of the recited stages of breast cancer. With respect to the ability for a single gene to be expressed in correlation with all three of the recited stages, Applicants respectfully point out that this is a possibility where a single gene is expressed in all three of the stages relative to normal cells. This is consistent with the description of the invention as supported by the instant application. Accordingly, the rejection of claim 20 appears misplaced and may be withdrawn.

With respect to claim 21, Applicants thank the Examiner for pointing out a clerical error that may have led to the inclusion of the claim in the instant rejection. That error has been corrected, and so the inclusion of claim 21 may be withdrawn.

In light of the foregoing, Applicants respectfully submit that this rejection may be properly withdrawn for the reasons provided above.

Claim Rejections under 35 USC § 102

Claims 15-21 and 30-32 were rejected under 35 USC § 102(e) as allegedly anticipated by Sioto et al. (USP 6,673,024)

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present with respect to the instant claims. Simply put, Sioto et al. do not teach all the requirements of the claims.

As an initial matter, and with respect to claim 20 and new claims 39-43, Sioto et al. fail to disclose or suggest any gene sequence the expression of which is correlated with ADH, DCIS, or IDC as required by claim 20. As such, it is simply not possible for Sioto et al. to anticipate these claims. Accordingly, this rejection should be withdrawn at least with respect to claim 20 (and recognized as not applicable to new claims 39-43).

With respect to claims 15-19, 21, and 30-32 as well as new claims 33-38, Applicants point out that contrary to the allegation of Sioto et al. disclosing the use of specific markers, Applicants respectfully point out that none of the following markers (mentioned by Sioto et al.) are recited in any of Tables 2-5 of the instant application: EGFR, p53, HER-2 neu, CEA, PSA, ErbB2, LDH, and GCDFP-15. Accordingly, Sioto et al. cannot anticipate any of the instant claims because there is no disclosure or suggestion for the use of any five or more gene sequences as provided by the instant invention.

Instead, Sioto et al.'s disclosure of the estrogen receptor, the sole recitation of the gene for "estrogen receptor 1" in instant Table 3 is not material to the use of five or more genes as provided by the instant invention.

In light of the foregoing, Sioto et al. simply do not disclose or suggest any method encompassed by claims 15-19, 21, and 30-32 or new claims 33-38. Accordingly, no *prima facie* case of anticipation is present against claims 15-21 and 30-32. Applicants respectfully submit that this rejection may be properly withdrawn.

Claims 15-21 and 30-32 were rejected under 35 USC § 102(e) as allegedly anticipated by Hung (USP 6,642,009).

Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse because no *prima facie* case of anticipation is present with respect to the instant claims. Simply put, Hung does not teach all the requirements of the claims.

As an initial matter, and with respect to claim 20 and new claims 39-43, Hung fails to disclose or suggest any gene sequence the expression of which is correlated with ADH, DCIS, or IDC as required by claim 20. Contrary to the statement of the instant rejection, the discussion from column 9, line 52, through column 10, line 14, provides no guidance for the practice of the invention as claimed. The discussion in column 9 merely discusses the use of cytological evaluation to determine cells as being ADH or one of two grades of DCIS. The discussion in column 10 merely sets forth the possibility of a marker "capable of distinguishing between any two cytological categories". Applicants respectfully point out that no examples of such markers are disclosed.

The listing of markers from column 6, line 53, to column 9, line 37, does not include any that are disclosed as being capable of distinguishing between ADH, DCIS, or IDC and another stage as encompassed within the scope of claim 20 and new claims 39-43. To the contrary, the list includes speculative markers, such as "Lg" (column 7, lines 1-4) which refers to a hamster lacrimal gland female-specific major 20 kDa secretory protein (see attached abstract from Ranganathan et al.). Applicants respectfully submit that at best, such a protein would only be relevant in cases of breast cancer, and ductal lavage or fine needle aspiration samples, in hamsters.

As such, it is simply not possible for Hung to anticipate these claims. Accordingly, this rejection should be withdrawn at least with respect to claim 20 (and recognized as not applicable to new claims 39-43).

With respect to claims 15-19, 21, and 30-32 as well as new claims 33-38, Applicants point out that contrary to the listing of markers from column 6 to 9 as described above does not include five or more genes as disclosed in any one of Tables 2-5 of the instant application. Applicants review of the Hung list reveals the possibility of only 4 genes being part of instant Tables 2-5: the nuclear matrix 23 (nm23) marker (in column 7, lines 63-67 of Hung and possibly in instant Table 2); the complement regulatory protein CD 59 marker (in column 8, lines 22-25 of Hung and possibly in instant Table 3); the catechol-O-methyltransferase marker (in column 9, line 20 of Hung and possibly in instant Tables 2, 4, and 5); and the kallikrein 6 marker (column 9, lines 31-37 of Hung and possibly in instant Tables 2, 3, and 4).

Thus even assuming *in arguendo*, and with the reservation that Hung possibly does not actually disclose the use of the genes of Tables 2, 3, 4 and 5 as discussed above, that the above Hung markers are those disclosed in the respectively identified Tables, there is still no disclosure of the use of five or more genes of any one of the Tables as required by the instant claims.

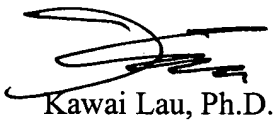
Therefore, Hung simply does not disclose or suggest any method encompassed by claims 15-19, 21, and 30-32 or new claims 33-38. Accordingly, no *prima facie* case of anticipation is present against claims 15-21 and 30-32. Applicants respectfully submit that this rejection may be properly withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100 .

Respectfully submitted,



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J Steroid Biochem Mol Biol. 1999 Sep-Oct;70(4-6):151-8.

Hormonal effects on hamster lacrimal gland female-specific major 20 kDa secretory protein and its immunological similarity with submandibular gland major male-specific proteins.

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Centre for Cellular and Molecular Biology, Hyderabad, India.

Hormonal regulation of a major 20 kDa protein of hamster exorbital lacrimal gland (LG) was studied by SDS-PAGE profile analysis and the purified protein's antisera was used to screen tissues of hamster and other species for crossreacting proteins. This protein was seen in female LG but not in males and late-pregnant or hCG-treated females. Low estrogen state in females after gonadectomy, prolonged light-deprivation, prolonged starvation or lactation increased its level several folds to approximately 20% of LG soluble proteins and similar levels were induced in males after gonadectomy (low androgen state). However, light-deprivation or melatonin treatment-induced low androgen state in males had no effect. In gonadectomized hamsters, this LG protein was obliterated on treatment with androgens, estrogens or thyroid hormones. Only estrogen inhibition of LG 20 kDa was prevented by simultaneous tamoxifen administration. Simultaneous treatment of gonadectomized hamsters with gonadotrophins and estrogen/androgen did not prevent the LG 20 kDa protein's inhibition. Relative potencies of estrogens (3.6 microg daily dose) were: estradiol-17beta approximately diethylstilbestrol > estrone > estradiol-17alpha, while estriol and chlorotrianisene had no effect. Dexamethasone, progesterone, prolactin, hypothyroid state or adrenalectomy had no effect on LG 20 kDa expression. Western blot studies confirmed the marked repression of LG 20 kDa by estrogen androgen and thyroid hormone and detected the protein in tears of females and gonadectomized hamsters but not in males. Interestingly, among other tissues tested, crossreaction was only seen with the estrogen-repressed 24 and 20.5 kDa major male-specific secretory proteins of hamster submandibular glands (SMG) which were previously reported by us. This strongly indicated that the LG and SMG proteins are products of the same or closely related genes. A possible role for these hamster sex-specific LG and SMG major secretory proteins in olfactory communication is suggested.

PMID: 10622403 [PubMed - indexed for MEDLINE]